Analgesic and Cognitive Effects of Intravenous Ketamine-Alfentanil Combinations Versus Either Drug Alone After Intradermal Capsaicin in Normal Subjects

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Combinations of opioids and *N*-methyl-D-aspartate (NMDA) antagonists enhance acute antinociception and reduce opioid tolerance in some animal experiments but have received little rigorous study in humans. To quantitatively assess the nature of the interaction of these two classes of drugs in producing analgesia and cognitive impairment, we compared IV infusions of ketamine, alfentanil, and ketamine-alfentanil combinations in 12 normal volunteers after an intradermal injection of capsaicin. Drug doses for a 70-kg subject in this six-session, randomized, double-blind, cross-over study were: ketamine 20 mg, ketamine 5 mg, alfentanil 2 mg, alfentanil 0.5 mg, ketamine 10 mg + alfentanil 1 mg, and ketamine 2.5 mg + alfentanil 0.25 mg, given over 35 min. Outcome measures were background pain, area and magnitude of hyperalgesia to pinprick, and cognitive performance on the Digit Symbol Substitution Test and the Perception Speed Test. The results demonstrated simple additivity for the effects of ketamine and alfentanil on pain, pinprick hyperalgesia, and cognitive impairment. We conclude that, at least in this experimental pain model, there is no clear advantage or disadvantage of a ketamine-alfentanil combination over equianalgesic doses of either component. **Implications:** In a double-blind, controlled trial, we administered doses of an opioid analgesic (alfentanil), an *N*-methyl-D-aspartate receptor antagonist (ketamine), or their combination to normal volunteers and found no advantage of the combination over a larger dose of either drug alone in relieving pain caused by painful chemical stimulation.

(Anesth Analg 1998;86:1250–6)

The idea of combining an antagonist of the *N*-methyl-D-aspartate (NMDA) glutamate receptor with an opioid has excited considerable interest in analgesia research. One goal of using such a combination would be to increase analgesia more than side effects. Because opioids and NMDA receptor antagonists have some overlapping toxicities, including sedation and nausea, a favorable clinical outcome might require a strong analgesic interaction of the drug classes.

Chapman and Dickenson (1) reported that intrathecal morphine and 7-chlorokynurenate, an antagonist at the glycine site of the NMDA receptor, were synergistic in reducing windup of rat dorsal horn neurons evoked by C-fiber strength electrical stimulation of the hindpaw. Silviotti et al. (2) proposed a mechanism for synergy with their observation that C-fiber stimulation causes four distinct waves of depolarization in rat spinal cord slices, of which the third is readily blocked by NMDA receptor antagonists and the fourth by morphine. Other investigators have reported that the analgesic interaction between NMDA antagonists and opioids is additive rather than synergistic—Yamamoto and Yaksh (3) for the intrathecal combination of MK-801 with morphine in the chronic constriction injury model of neuropathic pain in rats, Yamamoto et al. (4) for the carrageenan model of acute inflammation in rats, and Dambisya and Lee (5) for systemic ketamine and morphine in the tail-flick assay in mice. Several other laboratories have focused on another possible role for NMDA antagonist-opioid combinations, finding that NMDA receptor antagonists prevent or reverse opioid tolerance (6) and reduce opioid-induced hyperalgesia.

Controlled studies in humans suggest that the systemic administration of NMDA receptor antagonists

Accepted for publication March 3, 1998.

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0003-2999/98/$5.00

such as ketamine or dextromethorphan reduce acute experimental pain, postoperative pain, and chronic neuropathic pain (7,8), but cognitive and dissociative side effects usually preclude the use of sufficient doses to achieve complete relief. A handful of studies have evaluated the practical benefits of adding systemic NMDA receptor antagonists to opioids, although none were designed to determine whether the analgesic interaction was synergistic, additive, or subadditive. Of five published studies of ketamine-opioid combinations in postoperative pain, one (9) describes a marked reduction in pain, nausea, urinary retention, itching, and supplemental opioid dose with the combination compared with either opioid alone, and four other studies (10–13) describe approximately equal analgesia and toxicity for the combination and the opioid alone. Four published reports of systemic ketamine-opioid combinations in cancer, three single case reports (13a,13b,13c) and one 18-patient case series (14), describe dramatic improvement in patients who had suffered intractable pain with opioids alone.

The current study examines the nature of the ketamine-alfentanil interaction for both pain relief and for cognitive impairment, reasoning that a favorable finding of a greater degree of additivity for analgesia than for cognitive impairment would encourage therapeutic research with these combinations. Although ketamine acts on a number of receptor systems, NMDA receptor blockade is probably the predominant analgesic mechanism relevant to small IV doses of ketamine (15). We chose the capsaicin model because of the strong evidence that this stimulus produces central sensitization (16) that may be mediated in part by NMDA receptor activation, the similarity of the capsaicin-evoked burning pain, allodynia, and hyperalgesia to symptoms described by patients with chronic neuropathic pain, and the convenience of an experimental pain model for the extensive dose-finding experiments needed to select a promising regimen before clinical trials (17).

Methods

Twelve normal subjects completed a six-session, randomized, double-blind, cross-over study comparing the effects of six different drug infusions on capsaicin-evoked pain, pinprick hyperalgesia, and cognitive function. Figure 1 describes the timeline for experimental procedures and observations. A 70-kg subject received the infusions shown in Table 1. Drug doses were adjusted proportionally for weight and were administered over 35 min.

The larger doses of ketamine and alfentanil alone were based on the doses that produced reductions in pain, pinprick hyperalgesia, and mechanical allodynia of 50%–75% in a previous study (17). Drug doses in that study were individually titrated until side effects appeared. Because we wished to use fixed dose ratios for the treatments, we eliminated individual titration and reduced the mean doses from the previous study (ketamine 32 mg and alfentanil 3.1 mg) by approximately one-third to ensure that the subjects could tolerate them.

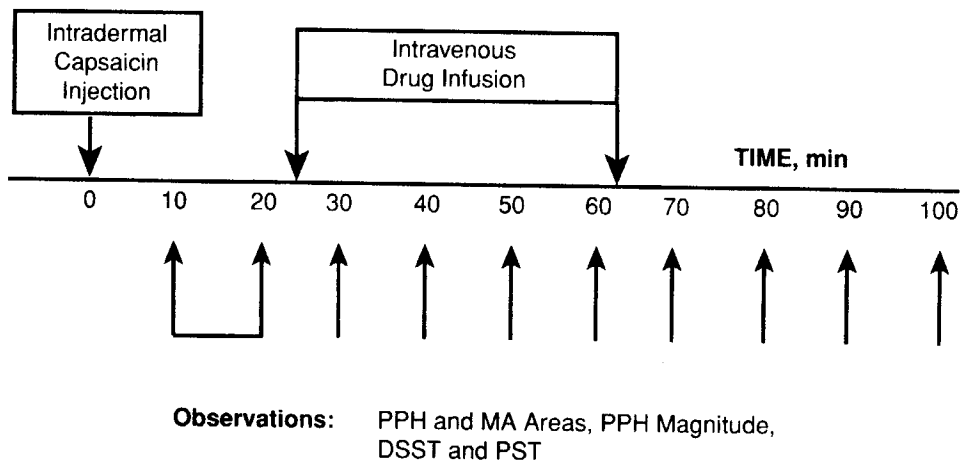

Figure 1. Timeline of experimental procedures. PPH = pinprick hyperalgesia, MA = mechanical allodynia.

Table 1. Drug Treatments

	Doses (mg)		
	Alfentanil	Ketamine	Combination[a]
Large-dose	2	20	10 + 1
Small-dose	0.5	5	2.5 + 0.25

All doses were adjusted linearly according to weight. The doses shown above are those given to a 70-kg subject.

[a] The dose of ketamine + alfentanil is shown.

The six treatments comprised a large-dose and small-dose triad of infusions, the two sets of doses being separated by a factor of 4. Within each triad, the combination consists of one half of the dose of each drug alone. Plummer et al. (18) and Laska et al. (19) proposed that each of these triads represents the simplest set of treatments that may be used to test for synergy. A result that the effect of the combination is significantly greater than each component, as demonstrated by two *t*-tests, is sufficient to prove synergy (19). We elected to study two triads of doses to make it more likely that if synergy were present, we had selected the most appropriate range in which to demonstrate it.

This study design is based on the same principles that underlie the standard method used to examine drug combinations for synergy, the isobolographic method (19–21). The isobolographic method involves the determination of full dose-response curves for each component and for the combination. From each dose-response curve, one determines the dose that produces half of the maximal possible effect (ED_{50}) (20). One then plots the ED_{50} values for each component and the combination on a graph whose two axes represent the dose of the two components. A line

connecting the two points representing the ED_{50} values for the single components connects all of the dose combinations that would be at the ED_{50} if the components had exactly additive effects. One demonstrates synergy by showing that the point representing the actual doses for the ED_{50} of a combination lies significantly closer to the origin than this additive line.

Although the isobolographic method is valid and well known and the results are displayed in a readily understandable graph, this approach has disadvantages, most notably the large number of patients required. If one uses 3-point dose-response curves and tests each drug alone and one dose ratio of a combination, nine treatments must be studied. We wished to use a complete cross-over study, which is efficient because it eliminates much of the interindividual variability in response to capsaicin and drug distribution, but few of our subjects would agree to more than six or seven sessions, which ruled out a traditional isobolographic design. An additional advantage of the Plummer-Laska method is that one can use continuous variables, in contrast to the isobolographic method, in which all of the data from each subject's experimental session are reduced to a single dichotomous variable used to determine an ED_{50} value (20). Preservation of the continuous variable and the information that it represents may increase the experiment's power, thereby reducing sample size. The use of this test is most effective when data allows the selection of doses of the individual drugs that are approximately equieffective; if the doses of the two drugs alone have widely disparate effects, it may require a strong degree of synergy for the combination to demonstrate superiority to the more effective component.

Subjects were paid healthy volunteers. They granted informed, written consent for the study, which had been approved by our review board.

Capsaicin solution 10 mg/mL was prepared according to the method of Simone et al. (22), from powder (Fluka, Ronkankoma, NY). Capsaicin 250 μg was injected using a 0.5-mL syringe fitted with a 27-gauge 3/8-in. intradermal beveled needle. Simone et al. (22) reported that the vehicle solution alone produced little or no pain and no other sensory abnormalities.

Each subject received seven intradermal injections of capsaicin during the study, one during a preliminary session and six during the actual experiment. The first injection was performed in the midline of the volar forearm approximately 5 cm proximal to the wrist creases. The subsequent injections were randomly assigned among six sites along the radial and ulnar distribution, each site spaced 2–3 cm proximal to the previous injection. Movement of the injection site is necessary because capsaicin injections desensitize primary afferents at the immediate site of injection. The minimal time between test sessions was 24 h. At every session, subjects were examined to exclude the possibility of allodynia and hyperalgesia persisting from the last injection. No time effect on capsaicin-evoked pain, hyperalgesia, or allodynia from one session to another was noted in a previous study that used the same precautions (17).

For the first 10 min after capsaicin injection, the ongoing pain level was assessed at 2-min intervals using a 100-mm vertical visual analog scale (VAS) whose anchor points were "no pain" and "worst pain." At 10 min after capsaicin injection, and then at 10-min intervals through 100 min, the following sequence of observations were performed.

1. Background pain rating using the 100-mm VAS.
2. Mechanical allodynia, assessed by lightly dragging a 2 × 2-in. cotton gauze pad back and forth four times along the skin between the points 2.5 and 5 cm proximal to the injection site. Subjects were asked to describe how unpleasant the sensation caused by the stroking was using the 100-mm VAS.
3. Magnitude of pinprick hyperalgesia (PPH) was tested using a safety pin weighted to elicit a sharp sensation that was just short of causing pain before the capsaicin injection. The pin was applied at the 2.5-cm mark, and subjects rated pain intensity on the VAS.
4. To measure the area of allodynia, a cotton gauze pad was swept at 1 cm/s toward the injection site starting approximately 10 cm away. This was repeated to form a pattern of eight radial spokes. With movement along each spoke, the subject was asked to report when the sensation became "different and unpleasant," and this spot was marked.
5. Using the same pattern of eight radial spokes to produce a plot of the area of pinprick hyperalgesia, a standard safety pin was applied until dimpling of the skin was just visible to measure the area of pinprick hyperalgesia. The subject was asked to report when the sensation became "different and painful," and the spot was marked.
6. To measure cognitive function, subjects performed two paper-and-pencil tasks, the Digit Symbol Substitution Test (DSST) and the Perception Speed Test (PST).
7. To assess side effects, subjects were asked, "Do you feel any effects of the medication?" For a global assessment of intoxication, the subject was asked, "Do you feel able to drive a car competently, despite any drug effects that you may feel?" The subject was then asked whether he or she noted any of a standard list of side effects and was invited to volunteer any other symptoms.

At 25 min after the capsaicin injection, just after completion of the 20-min observations, drug infusions

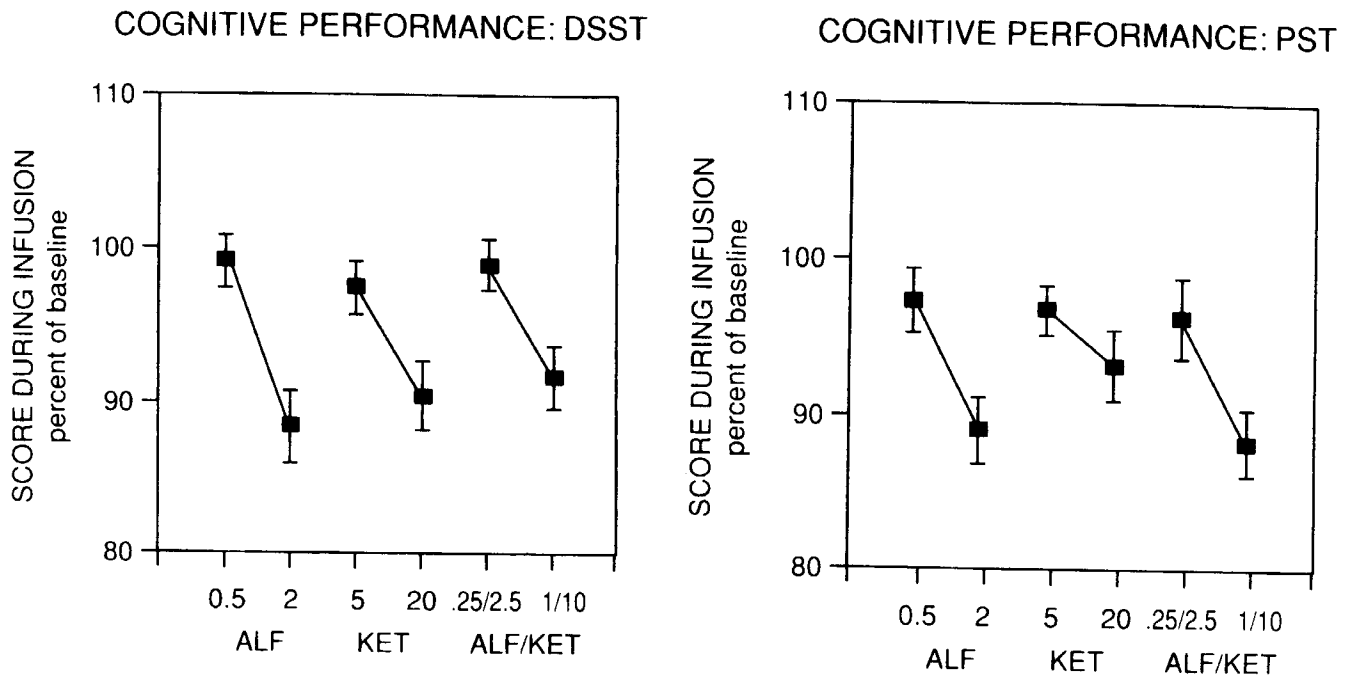

Figure 2. Cognitive function during and just after drug infusion, as measured by using the Digit Symbol Substitution Test (DSST, left) or the Perception Speed Test (PST, right), as a percentage of the baseline (mean of values at 0, 10, and 20 min). Error bars represent standard errors of the mean. Effects of the combination are additive relative to alfentanil or ketamine alone. ALF = alfentanil, KET = ketamine, ALF/KET = alfentanil/ketamine combination.

were begun (Table 1). Of the total dose, 14% was infused as a loading bolus over the first 3 min, and the remaining 86% was infused over the next 32 min using a Medfusion 2010 infusion pump (Medex Inc., Duluth, GA).

If the area of PPH 20 min after the capsaicin injection was <5 cm^2, no infusion was given, and the subject returned on another day. If this poor response occurred three times for the same subject, the subject was excluded from the study. Hyperalgesia rather than mechanical allodynia was used for this minimal entry criterion because previous work suggests that the occurrence of allodynia is more variable than hyperalgesia (17). After the experiment, the points defining areas of hyperalgesia and allodynia were traced onto an acetate sheet and connected to form a polygon whose area was determined by using a computer.

Based on our previous study of ketamine and alfentanil (17), the protocol defined the primary outcome measures as the mean areas or intensities of pain or hyperalgesia and cognitive testing scores, averaged over the four measurements performed during and just after the infusion (30, 40, 50, and 60 min). These scores were expressed as a percentage of postcapsaicin, preinfusion baseline scores, defined as the mean of the 10- and 20-min observations for that experimental session. This normalization procedure corrects for much of the interinjection variability in the sensory changes produced by capsaicin and increases the sensitivity of the method (17).

To test for departures from additivity (synergy or subadditivity), the scores for each combination treatment were compared with the scores for each component of that treatment using paired *t*-tests (18,19).

Results

Twelve subjects, 10 men and 2 women aged 20–26 yr, completed the six-session experiment. In addition, 10 subjects underwent one or more sessions but did not complete the study for the following reasons: 3 subjects did not develop the 5-cm^2 area of PPH on two or three consecutive capsaicin injections; 3 found it difficult to cooperate with psychophysical testing during test doses of ketamine; 2 found the capsaicin-induced pain too severe to return for six more sessions; 1 developed an urticarial lesion at the site of the capsaicin injection 6 h later; and 1 dropped out for personal reasons.

Figure 2 shows the effects of the drug treatments on the DSST and PST. Alfentanil, ketamine, and their combination impaired performance on each of the tests in a dose-dependent manner (Table 2; differences between doses were statistically significant in all cases except for ketamine alone on the PST). Neither dose of the combination reduced the DSST score more than each of two drugs alone (at the corresponding dose level) for either test. Each dose level of the combination reduced performance on the PST more than their respective components, but none of the differences were statistically significant ($P = 0.19$ for the large-dose combination versus ketamine; $P = 0.79$ for the large-dose combination versus alfentanil; $P = 0.87$ for the small-dose combination versus ketamine; and $P = 0.79$ for the small-dose combination versus alfentanil using two-tailed *t*-tests). Therefore, synergy was not demonstrated at these dose levels.

There were trends toward dose-dependent reductions of ongoing pain and the magnitude and area of PPH during the drug infusions, with the exception of the PPH area during ketamine alone (Figure 3). Because of large standard errors in these data points, however, none of the dose-response relationships were statistically significant (Table 2). Neither dose of the combination reduced background pain or the PPH magnitude more than each of the two drugs. The small dose of the combination reduced the PPH area slightly more than either of the components, but neither of these comparisons were statistically significant ($P = 0.93$ and 0.88 for the small-dose

combination versus ketamine and versus alfentanil, respectively). Therefore, synergy was not demonstrated at these dose levels.

The occurrence and degree of mechanical allodynia before drug infusion was extremely variable. No subjects met our threshold criterion of 5 cm^2 of allodynia for all six sessions, and six subjects had essentially no allodynia in any session. For this reason, the allodynia data were not sufficient to examine the nature of the ketamine-alfentanil interaction. Side effects of the drug treatments are presented in Table 3.

Discussion

Our data suggest a simple additive interaction for systemic ketamine and alfentanil in the reduction of capsaicin-evoked pain and PPH and for impairment on two paper-and-pencil cognitive tasks, the DSST and the PST. This suggests that Chapman and Dickenson's (1) finding of a synergistic analgesic interaction between an intrathecal NMDA antagonist and opioid in an animal model of windup does not generalize to systemic drug administration in this human pain model. Our data is more in accord with other animal (3–5) and human studies (10–13) that suggest additive interactions.

There are several reasons to be cautious about the present data. First, although we used a within-subject cross-over design to decrease the variability in this experimental pain model, there was still a large degree of variability in the occurrence of pain, hyperalgesia, and allodynia. We were also disappointed that mechanical allodynia occurred inconsistently and therefore could not be meaningfully analyzed, although we had observed similar variability in our previous study (17). We have subsequently shown that much of the variability in allodynia and hyperalgesia can be eliminated by screening out minimal responders before beginning the studies and by fixing the skin temperature at 36°C with a feedback-controlled heat lamp (23), rather than letting it vary within its usual range of approximately 28–32°C. A fixed skin temperature is important because capsaicin-related pain and hyperalgesia increase with skin temperature (23).

Because the variances in pain measurements in the present study are large (Figure 3), we cannot completely rule out the possibility that synergy exists for this combination; the 95% confidence intervals for all of the pain variables include points that are lower than those of both components of the combination. The test for synergy would have been statistically significant only if the combination had reduced the PPH area by approximately 20 percentage points (Figure 3) and PPH magnitude and background pain by approximately 40 percentage points relative to each component alone. However, the data do not seem to even

Table 2. Significance Levels for Dose-Response

	Cognitive function		Sensation		
Drug	DSST	PST	Pain	PPH area	PPH magnitude
Alf	0.002*	0.003*	0.36	0.06	0.16
Ket	0.02*	0.16	0.47	0.36	0.25
Ket + Alf	0.02*	0.014*	[a]	0.17	0.27

PPH = pinprick hyperalgesia, DSST = Digit Symbol Substitution Test, PST = Perception Speed Test, Ket = ketamine, Alf = alfentanil.

* Statistically significant dose-response relationship (paired t-test, one-tailed).

[a] The smaller dose apparently had a greater effect than the larger dose.

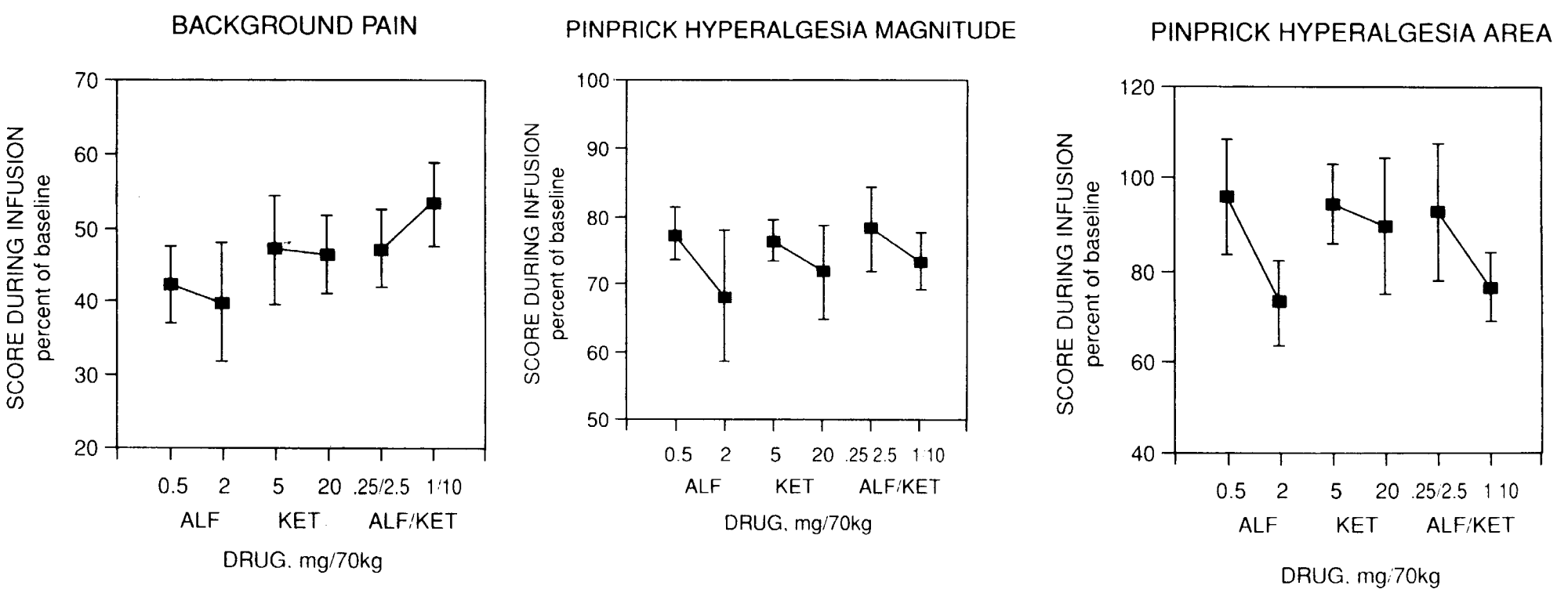

Figure 3. Background pain (left), pinprick hyperalgesia magnitude (center), and pinprick hyperalgesia area (right) during and just after drug infusion, as a percentage of the baseline (mean of scores at 10 and 20 min). Error bars represent standard errors of the mean. Effects of the combination are approximately additive relative to alfentanil or ketamine alone. ALF = alfentanil, KET = ketamine, ALF/KET = alfentanil/ketamine combination.

Table 3. Side Effects in 12 Subjects Who Received All Six Infusions

Treatment (mg)	Sense of intoxication[a]	Dizziness	Blurred vision	Itching	Nausea	Unreal or "spacey"
Alfentanil						
0.5	10	9	2	2	4	—
2	10	12	3	4	1	1
Ketamine						
5	10	10	6	4	1	2
20	9	10	3	1	1	1
Alfentanil + Ketamine						
0.5 + 2.5	11	9	5	3	2	—
1 + 10	9	9	4	3	4	—

[a] Determined by a negative response to the question, "Do you feel able to drive a car competently?"

suggest a trend toward synergy. In fact, the data points for the combinations are quite close to the means of the values for their two component drugs, the predicted values for simple additivity if dose-response curves for each component drug were linear [an assumption that is not required in the isobolographic method (20) or the Plummer-Laska variant that we used (18,19)].

As with any experimental pain model, the degree of generalizability to clinical pain states is arguable. In the few cases in which it is possible to compare drug responses in clinical neuropathic pain with those in experimental hyperalgesia evoked by capsaicin or mustard oil, responses have been similar (17,24,25), and more studies are required to determine the predictive value of these and other experimental pain models for efficacy in various clinical conditions. Although we find clinical data of a drug's efficacy more convincing than data from a laboratory model, well studied experimental human models might be a great boon to preliminary clinical pharmacology studies of single analgesics or combinations and to studies of pain mechanisms.

We administered drug treatments only after an intradermal capsaicin injection had established a hyperalgesic state. It is possible that the ketamine-alfentanil combination might have produced analgesic synergism if given preemptively, i.e., before the capsaicin injection. However, in a previous study (17), ketamine or alfentanil alone reduced capsaicin-evoked pain, allodynia, and hyperalgesia by approximately the same degree whether given before or after the capsaicin. We chose to administer the analgesics after capsaicin because the experimental variation was potentially lower [we could adjust pain and hyperalgesia during the infusion according to the baseline value produced by that capsaicin injection before drug infusion and could abort the experiment if capsaicin produced little hyperalgesia (17)] and because we were particularly interested in developing treatments for chronic pain, for which a postcapsaicin treatment may provide a better model.

If we have made accurate estimates of the additive nature of the ketamine-opioid interactions, and if this experimental model predicts response in at least some chronic pain conditions, these results do not show an obvious definite pharmacological advantage or disadvantage of a ketamine-opioid combination compared with a larger dose of one drug alone. In some clinical situations, such as with a patient with persistent pain despite opioid-induced respiratory depression, the additive analgesia produced by ketamine would be desirable in view of its relative lack of respiratory depression. The demonstration of an additional clinical advantage of such a combination, such as the reduction of tolerance to opioid analgesia produced by NMDA receptor antagonists in animals (6), could tip the scales toward the use of these combinations.

We thank Robert Caudle and Katerina Sawtelle for reviewing the manuscript.

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